Original Article

Transcranial Ultrasonography Doppler in Detecting Clinical Outcome of Term Neonates with Perinatal Asphyxia: A Longitudinal Study

JAYESH R SOLANKI[1], JANAKIRAM[2]

(cc) BY-NC-ND

ABSTRACT

Introducton: Perinatal asphyxia is one of the most important causes of mortality and morbidity in full-term neonates, where due to the hypoxic insult, mortality and various morbidities happens. So, it is important to predict both the outcomes to aid in patient management, as well as to counsel the caregivers regarding the outcome of the patient, especially the neurological outcome.

Aim: To determine the usefulness of abnormal Resistive Index (RI) values on transcranial USG doppler and its association with clinical outcomes in term neonates with perinatal asphyxia.

Materials and Methods: This prospective longitudinal study was conducted in the extramural Neonatal Intensive Care Unit (NICU) and Rukmani Chainani NICU of Sir Sayaji General (SSG) Hospital, Vadodara, Gujarat, India, from June 2020 to November 2021. Study was conducted among a cohort of 174 term newborns with perinatal asphyxia admitted in both intramural and extramural NICU of SSG Hospital Vadodara. Neurodevelopmental assessment was done by Amiel-tison scoring system, done at birth, at the time of discharge, at three and six months of age with simultaneous RI value monitoring by a trained radiology resident. The clinical association was done in terms of mortality at birth, morbidities encountered during the NICU stay and neurological outcome at six months of age. Development assessment was done by history taking and clinical examination, patients with delay in two or more domains were classified as global developmental delay, patients with delay in less than two domains were classified as mild developmental delay. Continuable variables were analysed using one-way Analysis of Variance (ANOVA). Categorical data were analysed with Pearson's Chi-square test. Significance was defined by p-values less than 0.05 using a two-tailed test.

Results: Out of 174 newborns enrolled, 97 patients had normal RI values at birth, and 77 patients had abnormal RI values. Forty-eight patients expired after birth, with 27% mortality, and among which 43 patients had abnormal RI values at birth, which was statistically significant (p-value <0.0001). The majority of the newborns with abnormal RI required invasive mechanical ventilation (n=62) and had persistent pulmonary hypertension of newborn (n=40), ventricular dysfunction (n=33), feed intolerance (n=17), acute kidney injury (n=19) and sepsis (n=27).

Conclusion: Transcranial Ultrasonography (USG) doppler in the calculation of RI at birth is a useful non invasive point of care method to determine immediate short-term outcomes in the form of mortality and short-term morbidities encountered during NICU stay.

INTRODUCTION

Neonates are exposed to various perinatal insults, among which birth asphyxia, contributes to a significant burden on neonatal mortality and morbidity [1-4]. Data published by the World Health Organisation (WHO) stated that four million babies die before one month, of which perinatal asphyxia and birth injury have contributed 29% [5]. The majority of neonatal deaths are contributed to developing countries [6]. India contributed to 1.2 million neonatal deaths every year, among which 25-27% of deaths were due to perinatal asphyxia, mainly within the first three days of life [7]. Among full-term neonates, perinatal asphyxia is the most important cause of mortality and morbidity. According to the World Bank (UN inter-agency group) in India, the current neonatal mortality rate is 20.3 [8]. The outcome of the neonates depends on the resuscitation immediately after birth. If resuscitation is received on time, the neonates recover without adverse outcomes [9]. In recent days, the establishment of the Neonatal Intensive Care Unit (NICU) has decreased the adverse outcome among neonates. Earlier the clinical neurological assessment was a standardised procedure for foetal distress. Its role has been focused on determining the neurological outcome at the early stage. Therefore, an early assessment would provide long-term prognostic information [10]. With the evolving science in the neurological examination, the clinical accuracy in determining the neurological outcome has been improved with the Amiel-Tison scoring, which helps identify the damage to the cortical control pathway and predict the major and minor neurodevelopmental problems [11].

The deterioration of the autoregulation of cerebral blood is seen in patients with severe asphyxia. Advancement in the imaging field, non invasive imaging methods like the doppler scan can be used at the bedside without disturbing the patient, in calculating the RI to predict and provide a long-term neurodevelopmental prognosis [12]. Very few studies are available for Resistive Index (RI) value correlation with neurological assessment but those studies have enrolled a lesser number of patients in their study and some other studies used Amiel-Tison scoring alone in the prediction of the complications of Perinatal asphyxia they lack RI value co-relation [13-15]. The present study aimed to determine the usefulness of abnormal RI values on transcranial Ultrasonography (USG) doppler and its association with clinical outcomes in term neonates with perinatal asphyxia.

MATERIALS AND METHODS

A prospective longitudinal study was conducted in the extramural NICU and Rukmani Chainani NICU of SSG, Vadodara, Gujarat, India, from June 2020 to November 2021. Approval was obtained from the Institutional Ethics Committee (approval letter no. IECBHR/117-2020). A consent form was taken from parents at the time of enrolment of neonates.

Sample size calculation: Conventional sampling method was followed. As per institutional statistics of previous years, 200 neonates were expected to enrol but due to Coronavirus Disease 2019 (COVID-19) pandemic total number of enrolments was reduced to 174.

All the full-term neonates with perinatal asphyxia getting admitted in both extramural and intramural NICUs within 72 hours of life were enrolled in the study.

Inclusion criteria: Full-term neonates admitted to NICU fulfilling any one of the criteria given below:

- Baby does not cry immediately after birth with clinical signs of perinatal asphyxia

- Slow/gasping breathing or an Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score of 4-6 at 1 minute

- Persistence of low Apgar scores of less than 3 for more than 5 minutes

- Need for positive pressure ventilation for more than one minute

- Evidence of hypoxic ischemic encephalopathy based on clinical classification of perinatal asphyxia

Exclusion criteria:

- Neonates getting admitted after 72 hours of life

- Preterm neonates having gestation less than 37 weeks as calculated by new Ballard scoring [16]/Last Menstrual Period (LMP) wise/ sonographic dates whatever is available, as the possibility of outcome may be influenced by other factors specific to the preterm neonates

- Neonates receiving therapeutic hypothermia

- Patients with major congenital malformation

- Parents not giving consent for the study participation

In this study, 174 neonates were enrolled, analysed and followed-up.

Study Procedure

After taking informed written consent from the parents' the neonate underwent transcranial USG doppler at less than 72 hours of age admission by a trained radiology resident/consultant radiologist using pulse wave doppler ultrasound (Portable Mindray USG machine, Model M7, Serial no- CAQ99005578) with 3.5 MHz transducers available in NICU [Table/Fig-1] and RI was calculated and the same thing was done at discharge, at three months and at six months of age. Neonatal encephalopathy grading at birth was done by Levene's grading system [17]. The neurological assessment was done and recorded by the Amiel-Tison scoring system at the time of admission and at the time of discharge, three months and six months of age, along with that developmental assessment was done by history taking and clinical examination, patients with two or more domains were classified as global developmental delay, less than two domains involved were classified as mild developmental

delay and rest of the patients had normal development (domains included- fine motor, gross motor, social, language) [17].

Amiel-Tison's neurological examination predicts neurodevelopmental outcomes in term as well as preterm neonates. Each patient underwent this scoring system and a qualitative assessment of the neurological status of the patient was done along with a developmental assessment. Five important contributors to the scoring system namely are cranial assessment, neurosensory function and spontaneous motor activity, passive and active muscle tone and primitive reflexes. Feeding autonomy as well as the medical status at the time of examination was also considered while performing this scoring system [17].

The following components of the Amiel-Tison assessment score system were done at birth, at discharge, and at three and six months of age with simultaneous assessment of colour doppler USG and RI was done by trained consultant radiologist/radiology resident doctor with 0.6 to 0.8 taken as normal [Table/Fig-1] [15].
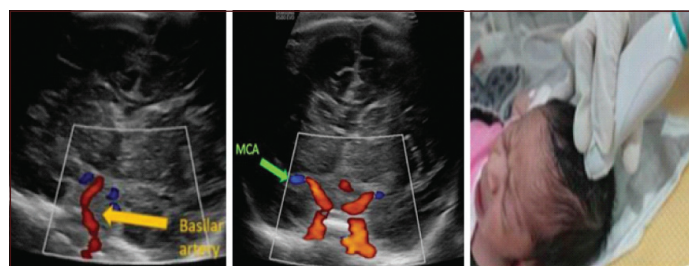
[Table/Fig-1]: Showing the calculation of RI values in cranial vessels using USG probe.

The components of neurological assessment include almost 35 items clustered into various domains [17]:

- Cranial assessment and neurosensory function and spontaneous motor activity.

- Assessment of passive muscle tone and active motor activity.

- Primitive reflexes and adaptiveness during the time of examination

- Medical status at the time of examination

STATISTICAL ANALYSIS

All statistical calculations were done using computer software International Business Machines Statistical Package for the Social Sciences (IBMSPSS) software version 21.0 (IBM-SPSS Science Inc., Chicago, IL). Data were statistically described in terms of mean/standard deviation. Categorical data were analysed with a Pearson's Chi-square test p-value of less than 0.05 was considered statistically significant. Continuous variables were analysed using one-way Analysis of Variance (ANOVA).

RESULTS

A total of 174 term neonates with perinatal asphyxia cases were enrolled and followed-up until six months of age. The mean birth weight in this study group was 2.65±0.427 kg (ranging from 1.7-4.2 kg), with the majority (n=77, 44.35%) in the age group of 2.6-3 kg, and since term neonates were enrolled in the present study, only 6 (3.45%) were <2 kg. In the present study, low birth weight (<2.5 kg) was seen in 65 patients (37.9%).

Among the total cases, mild asphyxia was there in 64 cases, 37 moderate asphyxia and 73 severe grade of perinatal asphyxia was there. At birth 64 (37%) patients had mild encephalopathy, 37 (21%)

patients had moderate encephalopathy, and 73 (42%) patients had severe encephalopathy secondary to perinatal asphyxia.

Among the total cases, 117 (67%) were males, and 57 (32%) were females. Since, the institute caters to surrounding areas, 139 (79.89%) were inborn, and 35 (20.11%) were outborn. The majority, 97 (55.7%) of the term neonates with perinatal asphyxia, had normal RI at birth and 77 patients had abnormal RI values. In comparison with the growth pattern, 95 (54.5%) were appropriate for gestational age, and 75 (43%) were small for gestational age; 4 (2.5%) patients were large for gestational age predominantly, patients with perinatal asphyxia were appropriate for gestational age, but it was not statistically significant (p-value=0.491).

Short-term morbidities: Comparing the RI with the need for invasive mechanical ventilation, the majority 62 (80.5%) of the cases had abnormal RI, and the majority of the cases with normal RI did not require invasive ventilation. As the RI value becomes abnormal, the requirement for invasive mechanical ventilation increases (p-value <0.0001).

In this study, 19 (17%) patients had acute kidney injury; on comparing with their RI, all the patients had abnormal RI (p-value<0.0001) [Table/Fig-2].

Resistive Index (RI)	Abnormal n (%)	Normal n (%)	p-value
Invasive mechanical ventilation required (N=82)	62 (75.61)	20 (24.39)	<0.0001*
PPHN (N=59)	40 (67.80)	19 (32.20)	<0.0001*
Ventricular dysfunction (N=42)	33 (78.57)	9 (21.43)	<0.0001*
Entral feed not started (N=46)	43 (93.48)	3 6.52)	<0.0001#
Feed intolerance (N=23)	17 (73.91)	6 (26.09)	0.002*
Convulsion (N=17)	9 (52.94)	8 (47.06)	0.448*
Acute kidney injury (N=19)	19 (100)	0	0.001#
Thrombosis of an arterial teritory (N=1)	1 (100)	0	0.26#
Sepsis (N=42)	27 (64.29)	15 (35.71)	0.003*

[Table/Fig-2]: Distribution of short-term morbidities in relation to Resistive Index (RI).
PPHN: Persistent pulmonary hypertension of the newborn; *Pearson chi-square test used; #Fisher-exact test; p-value in bold font indicates statistically significant values

In this study, only one patient had thrombosis of bilateral transverse sinuses and absence of myelination of the posterior limb of bilateral internal capsules; bilaterally symmetrical abnormal signal in bilateral lentiform nuclei and thalami; diffuse thinning of the corpus callosum, possibly due to hypoxic insult. The patient's initial RI was 0.90, which is abnormal, and then the patient was started on subcutaneous enoxaparin from the 45th day of life and patient had NICU stay for 59 days and was discharged on gavage feeds, but the patient got expired at four months of life due to aspiration pneumonia and septic shock.

On comparing the neurodevelopmental outcome with the RI value at birth, 103 (59%) patients got discharged successfully with normal

neurodevelopmental outcomes, among which a majority, 72 (77%) had normal RI values, and on discharge, all the patients had normal Amiel-tison scoring. Of the 48 neonates who expired (27% mortality) majority i.e., 43 (55.8%) of the patients had abnormal RI values, and 5 (5.2%) had normal RI values (p-value<0.0001). The majority of the patient with global developmental delay had abnormal RI values (n=7 out of 11 patients) [Table/Fig-3].

In this study, 23 (20%) of patients had abnormal neurodevelopmental outcomes among the discharged patients, according to Amiel-Tison neurological assessment.

DISCUSSION

In this study, the majority, 117 (67%) were males, showing the males predominance similarly, the studies conducted by Siva Saranappa SB et al., and Dongol S et al., had male predominance (male: female ratio of 2.3:1) (male:female ratio of 1.8:1) [18,19].

In this study, the mean birth weight was 2.65±0.427 similarly, in a study conducted by Kiyani N et al., the mean birth weight was 2.62±0.74 [20].

In this study, 82 (47%) required invasive mechanical ventilation, among which the majority of the patients had severe perinatal asphyxia and abnormal RI. In a study by Prakash R, conducted among term neonates with perinatal asphyxia, only 3 (2.5%) required invasive mechanical ventilation [21]. The discordance with the present study is because, in the study by Prakash R, only three patients had severe perinatal asphyxia, and all required invasive mechanical ventilation [21]. In a retrospective cross-sectional study conducted by Mat Bah MN et al., to look for the survival and risk factors for mortality among infants with persistent pulmonary hypertension of newborn, 65 (33%) had ventricular dysfunction, among which 60% survived after patients received inhaled nitric oxide, in this study 59 (34%) had Persistent Pulmonary Hypertension of the Newborn (PPHN) of which 42 (24%) patients had ventricular dysfunction, the prognosis was poor, the reason could be non availability of nitric oxide in the centre [22].

A study conducted by Kumar AS et al., to look for the prognostic value of RI in term neonates with hypoxic ischemic encephalopathy, enrolled 50 patients, among which 17 (34%) patients had culture positive bacterial sepsis out of which 12 (70%) patients had abnormal RI values at birth which was in concurrence to this study [14].

Assessment of neurodevelopmental outcome at six months showed a majority of 92 (80%) of the patients were discharged without developmental delay, 48 patients expired which happened within 72 hours of birth. In a study conducted by Kumar AS et al., 50 patients were enrolled, among which 44 patients got discharged, with a 12% mortality rate, and 50% of patients had abnormal neurodevelopmental outcomes at a 6-12 months follow-up period (n=17), which is comparable to the present study as out of 80 patients with abnormal RI values 56 (70%) patients had adverse outcome 43 patients expired at birth and 13 patients had developmental delay at six months of age [14].

Outcome analysis	RI	Discharged	Expired	Lost to follow-up	No delay	Mild delay	Global delay	p-value
At birth	Abnormal	24 (13.79%)	43 (24.71%)	0	0	6 (3.45%)	7 (4.02%)	<0.001
	Normal	79 (45.40%)	5 (2.87%)	0	0	6 (3.45%)	4 (2.30%)	
3rd month	Abnormal	0	43 (24.71%)	2 (1.15%)	28 (16.09%)	1 (0.57%)	8 (4.60%)	0.003
	Normal	0	5 (2.87%)	7 (4.02%)	66 (37.93%)	11 (6.32%)	3 (1.72%)	
6th month	Abnormal	0	43 (24.71%)	2 (1.15%)	36 (20.69%)	4 (2.30%)	6 (3.45%)	0.043
	Normal	0	5 (2.87%)	7 (4.02%)	58 (33.33%)	8 (4.60%)	5 (2.87%)	

[Table/Fig-3]: Association of neurodevelopmental outcome in relation to Resistive Index (RI).
Values are present as n (%)

In a study conducted by Prakash R, 120 patients were enrolled, and 26 (22%) patients had abnormal neurobehavior at discharge. 12 (7%) of patients had mild delay in milestones at six months [21]. According to Amiel-Tison neurological assessment, 6 (50%) had abnormal RI values, and rest had normal RI values at birth. Eleven (6.5%) patients had global developmental delay, out of which 7 (64%) patients had abnormal RI values at birth, and the rest (n=4, 36%), had normal RI values at birth.

In this study, 23 (20%) of patients discharged had abnormal neurodevelopmental outcomes according to Amiel-Tison neurological assessment. On comparing the clinical outcome of the neonates with the RI, there was a significant association and it was found to determine the outcome of the term neonates with perinatal asphyxia.

Limitation(s)

The Electroencephalogram (EEG) and neuroimaging were not possible in each patient to look for the precise long term neurodevelopmental outcome. Nine patients were lost to follow-up in the present study due to serial follow-up.

CONCLUSION(S)

The USG doppler along with simple neurological assessment can aid in the prediction of morbidities and mortality outcomes of neonates with perinatal asphyxia. So, authors recommend all primary care paediatricians gain expertise in both USG doppler and Amiel-Tison scoring system.

REFERENCES

[1] Md SO. Global burden of neonatal disease: caring for the world's most vulnerable patients 2017 newborn pediatric critical care conference.

[2] World Health Organization. WHO-MCEE Estimates for child causes of death 2000-2016.

[3] Lee AC, Mullany LC, Tielsch JM, Katz J, Khatry SK, LeClerq SC, et al. Risk factors for neonatal mortality due to birth asphyxia in southern Nepal: a prospective, community-based cohort study. Pediatrics. 2008;121(5):e1381-90.

[4] Velaphi S, Pattinson R. Avoidable factors and causes of neonatal deaths from perinatal asphyxia-hypoxia in South Africa: national perinatal survey. Annals of Tropical Paediatrics. 2007;27(2):99-106.

[5] Maternal and Newborn Health/Safe Motherhood Unit. Division of Reproductive Health (Technical Support). Basic Newborn Resuscitation: A Practical Guide. World health organization; 1997.

[6] Zupan J. Perinatal mortality in developing countries. N Engl J Med. 2005;(352):2047-48.

[7] Jena P, Parida H, Swain B, Murmu M. Study of perinatal asphyxia and its outcome concerning nucleated RBC count in venous blood of term neonates. Pediatric Review: International Journal of Pediatric Research. 2021;8(1):54-63.

[8] Estimates developed by the UN Inter-agency Group for Child Mortality Estimation. [Internet]. 2021. Available from: childmortality.org

[9] Aziz K, Lee CHC, Escobedo MB, Hoover AV, Kamath-Rayne BD, Kapadia VS, et al. Part 5: Neonatal Resuscitation 2020 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics. 2021;147:e2020038505E. https://doi.org/10.1542/peds. 2020-038505E

[10] Romeo DM, Bompard S, Serrao F, Leo G, Cicala G, Velli C, et al. Early neurological assessment in infants with hypoxic ischemic encephalopathy treated with therapeutic hypothermia. J Clin Med [Internet]. 2019;8(8):1247. Available from: http://dx.doi.org/10.3390/jcm8081247

[11] Gosselin J, Gahagan S, Amiel-Tison C. The Amiel-Tison Neurological Assessment at Term: conceptual and methodological continuity in the course of follow-up. Ment Retard Dev Disabil Res Rev [Internet]. 2005;11(1):34-51. Available from: http://dx.doi.org/10.1002/mrdd.20049

[12] Pishdad P, Yarmahmoodi F, Eghbali T, Arasteh P, Razavi SM. Using Doppler sonography resistive index for the diagnosis of perinatal asphyxia: a multi-centered study. BMC Neurol. [Internet]. 2022;22(1):104. Available from: http://dx.doi.org/10.1186/s12883-022-02624-2

[13] Abdo R, Halil H, Kebede B, Anshebo A, Gejo N. Prevalence and contributing factors of birth asphyxia among the neonates delivered at Nigist Eleni Mohammed memorial teaching hospital, Southern Ethiopia: a cross-sectional study. BMC Pregnancy Childbirth. 2019;(19):536.

[14] Kumar AS, Chandrasekaran A, Asokan R, Gopinathan K. Prognostic value of resistive index in neonates with hypoxic ischemic encephalopathy. Indian Pediatrics. 2016;53(12):1079-82.

[15] Jongeling BR, Badawi N, Kurinczuk JJ, Thonell S, Watson L, Dixon G, et al. Cranial ultrasound as a predictor of outcome in term newborn encephalopathy. PediatrNeurol [Internet]. 2002;26(1):37-42. Available from: http://dx.doi.org/10.1016/s0887-8994(01)00354-x

[16] Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr [Internet]. 1991;119(3):417-23. Available from: http://dx.doi.org/10.1016/s0022-3476(05)82056-6

[17] Gosselin J, Gahagan S, Amiel-Tison C. The amiel-tison neurological assessment at term: conceptual and methodological continuity in the course of follow-up. Mental Retardation and Developmental Disabilities Research Reviews. 2005;11:34-51.

[18] Siva Saranappa SB Nair CC, Madhu GN, Srinivasa S, Manjunath MN. Clinical profile and outcome of perinatal Asphyxia in a tertiary care center. Curr Pediatr Res. 2015;19(1&2):9-12.

[19] Dongol S, Singh J, Shrestha S, Shakya A. Clinical profile of birth asphyxia in Dhulikhel Hospital: A retrospective study. J Nepal Paediatr Soc [Internet]. 1970;30(3):141-46. Available from: http://dx.doi.org/10.3126/jnps.v30i3.3916

[20] Kiyani N, Khushdil A, Ehsan A. Perinatal factors leading to birth asphyxia among term new-borns in a tertiary care hospital. Iran J Pediatr. 2014;24(5):637-42.

[21] Prakash R. Clinical profile and neurobehavior at the discharge of term neonates with perinatal Asphyxia-a prospective observational study. International Journal of Contemporary Medical Research. 2016;3(10):3073-76.

[22] Bah M, Tan MN, Razak R, Sapian H, Abdullah MH, Alias N. Survival and associated risk factors for mortality among infants with persistent pulmonary hypertension of the newborn in Malaysia. J Perinatol. 2021;41(4):786-93.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Paediatrics, Medical College Baroda, Vadodara, Gujarat, India.
2. Junior Resident, Department of Paediatrics, Medical College Baroda, Vadodara, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Janakiram,
2-C, Pearl Residence, Lake Area, Madurai, Tamil Nadu, India.
E-mail: janakiramaks@gmail.com

AUTHOR DECLARATION:
• Financial or Other Competing Interests: None
• Was Ethics Committee Approval obtained for this study?   Yes
• Was informed consent obtained from the subjects involved in the study?   Yes
• For any images presented appropriate consent has been obtained from the subjects.   Yes